PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P9802		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO99/00143	03/05/1999	08/05/1998
International Patent Classification (IPC) or national classification and IPC C07K14/435		
Applicant NORSK HYDRO ASA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 16 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/12/1999	19.09.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Moonen, P Telephone No. +49 89 2399 8538

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NO99/00143

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-65 as originally filed

Claims, No.:

1-34 as received on 11/08/2000 with letter of 09/08/2000

Drawings, sheets:

1/14-14/14 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of th earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has

been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 20-24, 29 and 33.

because:

☒ the said international application, or the said claims Nos. 20-24, 29 and 33 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☒ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. partially 1, 16-34 and fully 2-15 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 16- 34 partially; 2-15 fully
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1, 16-34 partially; 2-15 fully
Industrial applicability (IA)	Yes:	Claims	1, 16-19, 25-28, 30-32 and 34 partially; 2-15 fully
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents (D), cited partially in the Search Report:

D1: WO 97 12992
D2: WO 96 18409
D3 Immunotechnology 2 (1996) 3-9 *
D4 Oncogene 16 (April1998) 1803-12 *
D5 Cancer Res 57 (1997) 1419-24 (abstract only) *
D6 Leukemia **11** (1997) 439-40 (abstract only) *
D7 Cancer Res **58** (March 1998) 997-1003, cited in the description *
D8 Cancer Res 57 (1997) 4420-4426 *
D9 Nature **382** (1996) 499-500 *
D10 Science **275** (1997) 1784-7, cited in the description *
D11 Ann Rev Immunol **12** (1994) 337-65, first page only *
D12 Hum Mutat **3** (1994) 347-352 (abstract only) *
D13 J Virology Dec 1997, 9410-6 (first page only)*
D14 Cancer Res **57** (1997) 2384-7 (abstract only) *
D15 J Hum Mol Genet **7** (Feb 1998) 195-202 (abstract only)*
D16 Cancer Res **58** (Feb 1998) 1124-6 (abstract only) *
D17 Cancer Res **52** (1992) 4168-74, cited by the Applicant *

* The documents D3-D17 were not cited in the international search report. Copies of the documents have been supplied to or by the Applicant, or are known to the Applicant.

Re Item I

Basis of the opinion

1. The new set of claims does not appear to refer to subject-matter extending beyond the originally filed application, except for claims 17, 28 and 32-34 with respect to the newly introduced wording "or a mutant protein as described in claim 1" or "of a DNA sequence encoding a protein as described in claim 1", respectively. Claim 1 refers only to a fragment of a mutant protein and chosen of sequences with ID NO:1-459, i.e. claim 1 does not refer to the full length mutant proteins per se. The subject-matter of mutant proteins is therefore presently not examined for claims 17, 28 and 32-34 although it is appears that page 12 would

provide a basis for clearly defined mutant proteins.

The separately numbered pages 1-79 of the sequence identity list have been taken into account.

Re Item II
Priority

2. In the present written opinion the document cited in the International Search Report as "P,X-document" has not been considered as the priority document is not available.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3. For the assessment of the present claims 20-24, 29 and 33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment

Claims 20-24, 29 and 33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion is formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Introduction:

4. The subject-matter of claim 1 of the present application is characterized by sequences selected from the listing presenting SEQ ID NOs:1-459, said sequences derived from a mutant part of a list of many different proteins and

should be capable of inducing T-cell responses. The mutation is a frameshift mutation in the coding part of a gene of a cancer cell (not limited to oncogenes or tumour suppressor genes; see present description page 9, lines 20-26). Mutant proteins resulting from a frame shift are known from the prior art.

Effective anti-tumor vaccines will in particular comprise **antigenic peptides** giving rise to **specific T cellular responses**: this feature about T cellular responses is **known from the prior art:**

A close prior art document is considered to be **D2**: this document refers to peptides of about 8-11 amino acids (derived from a tumor-associated protein, e.g. a mutated p53 protein, page 19) binding to (MHC) Class I molecules, expressed on cytotoxic T cells (CTLs) in relation to tumor theraphy (as alternative to the non-specific, IL-2 therapy) to strengthen or boost the cellular immune system. D2 also refers to peptides encoded by mutant genes as potential targets for T cell responses against tumor cells and their use in vaccines for malignancies (see page 4 lines 14-31). Mis-sense mutatations in p53 could be used in detection of small cell lung cancer patients (see page 19 lines 18-28, reference D17); D17 mentions also that no anti-p53 antibodies were detected in serum from one patient with a frameshift mutation: this does however not prove that other antibodies against the new sequence were not present in the serum (many patients having tumors with missense p53 mutations did not develop anti-p53 antibodies).

Reference is made on page 111 of D2 to Boon et al. (**D11**) who proposed that tumor antigens recognised by T cells fall into three categories, one of them being **novel sequences generated by point mutations**. **D5** refers to a **new sequence resulting of an in-frame deletion** (a **novel** epitope at the fusion junction). The full paper of D5 mentions in the introduction that "peptide vaccines based on point mutations such as those found in p53 or ras have been shown to elicit both a MHC class I and II response that will lyse target cells. However, any antitumor effects of these peptides has not been established in animal model systems, although it has been shown that immunization with whole mutant ras protein can elicit a therapeutic response". D5 demonstrates with the peptide vaccine (the peptide derived from the fusion junction) a regression of existing tumors.

Thus, the prior art has referred already to the concept of the present application concerning the idea of (small) peptides having (in part) novel sequence created by a mutation in a gene. **D1 refers to peptides** for use in diagnosis , the sequences of the peptide **characterised by a mutation arising from a frameshift mutation** (see page 5, 34 and the claims). D1 also mentions treatment of diseases associated with a gene having a frameshift mutation, the disease being e.g. cancer or a neurodegenerative disease (page 35, however no reference to a cancer vaccine is made). A relevant document referring to cancer vaccines (in relation to T-cell responses against mutant ras) is **D3**; the mutations leading to novel sequences being in this case substitutions in hotspots.

In conclusion, the prior art had already considered the use of peptides having novel sequences to stimulate specific T cellular responses. D1 refers to peptides having new sequences generated by frameshift mutations for use in diagnosis of a disease, and D2 and D5 refer to the use of novel sequences (although not resulting from a frameshift mutation, but from the two other possibilites to generate a new, disease-related sequence) in vaccines. No prior art is considered to be teaching away from the concept of using peptides resulting from frame shift mutations (referred to in D1) to stimulate specific T cellular responses.

5. An example of a frame-shift by a single base deletion is a BAX frameshift mutation (of a single residue in a sequence of 8 deoxyguanosine residues (G)8 tract within the BAX coding sequence) in cell lines derived from human haemopoietic malignancies (see **D4**, in particular Figure 6 and **D10**). Other articles had also referred to the mutations in simple repeated sequences as a mechanism for carciogenesis (microsatellite instability); see e.g. Rampino et al (Science 1997, cited in the description paragraph bridging pages 16-17; document **D10**) and Yamamoto et al (Cancer Research, March 1998, cited in the description page 19 lines 6-22; document **D7**).

It is therefore considered that the subject-matter of **claims 1 and 25** (as far as referring to the specified SEQ ID NOs of **restricted length** and not including full length mutant protein or the encoding DNA sequence) and the other claims on file are **novel** as far as they refer to the presently selected and examined 14 inventions. A special (new and inventive) technical feature (even when considered

in the perspective of the use of small peptides for use in tumor vaccines) is missing: the specifying of the (use of a) peptide containing in part a new sequence created by a frame shift resulting in a mutant gene is considered to be obvious in the light of D2 taking into account the fact that new sequences were known to be created by frameshift mutation (see D1), substitution (see D3), microsatallite instability (e.g. document D4) or deletion (see D5).

Re Item IV

Lack of unity of invention

6. The present International Preliminary Examining Authority has therefore identified in the present set of claims fourteen independent inventions represented by the peptides of claims 2-15 concerning all the frameshift mutations in the individually specified genes.

A single general inventive concept (referred to in Rule 13 PCT and the PCT Preliminary Examination Guidelines Ch.III, 7) is not recognisable in the absence of a common, special technical feature: the genes referred to in said claims have only in common the fact that they refer to a frameshift mutation and (poly)peptides resulting from such a mutation were already known in the prior art (for e.g. the BAX gene).

An invitation to restrict or to pay additional examining fees has been issued: the Applicant decided to pay 13 additional fees and filed a new set of claims representing the 14 inventions to be examined (claims 2-15).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

7. **Invention 1:** referring to the frameshift mutation in the BAX gene (altered in the amino acid sequence starting with position 41); SEQ ID NOs:1-12.

The peptides according to this invention are examplified in the description starting at the bottom of page 54. The peptides are all based on the deletion of one or

more nucleotides at codon 180 of the proapoptotic gene BAX already disclosed and studied by Brimmet et al. (D4); the group of Perucho et al (see D7-D9 and D10) has also referred to somatic frameshift mutations in the BAX gene in colon cancers. In view of these disclosures in the prior art it is considered that the specified sequences are obvious to the skilled person in the absence of any demonstrated unexpected effect. Therefore, the present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claim 2 (and part of claims 1, 16 and 34)** does not involve an inventive step (Rule 65(1)(2) PCT).

With respect to the (indirectly depending) **claims 17-33** it is considered that these claims in are obvious to the skilled person having the knowledge of D4 in combination with the teaching of e.g. D5 with respect to peptide vaccine based on novel epitopes resulting from a frameshift mutation.

8. **Invention 2:** referring to the frameshift mutation in the TGF-ß-RII gene (altered in the amino acid sequence starting with position 133 or 134); SEQ ID NOs:13-21 and 428 .

The peptides according to this invention are examplified in the description starting at the bottom of page 624.

The introduction of D10 reads as follows "The MMP (microsatellite mutator phenotype) pathway for colon cancer is characterised by genomic instability that leads to the accumalation of deletion and insertion mutations at simple repeat sequences. The fixation of these slippage-induced replication errors as mutations is associated with defects in DNA mismatch repair. Colorectal MMP+ tumors frequently contain **frameshift mutations in the type II TGF-ß receptor gene**". See also page 19 of the description with the reference to Yamamoto et al., D7).

The peptides of this invention all based on the known frameshift in the wild type RII cDNA repeat sequence of 10 adenines at nucleotides 709-718 are considered to be obvious in the light of for example D7 (reference can also be made to the earlier work of Wang et al., J Biol Chem **270** (1995) 22044-9) specifying already the frameshift. Therefore, the present application does not satisfy the criterion set

forth in Article 33(3) PCT because the subject-matter of **claim 3 (and part of claims 1, 16 and 34)** does not involve an inventive step (Rule 65(1)(2) PCT).

With respect to the (indirectly depending) **claims 17-3** it is considered that these claims in are obvious to the skilled person having the knowledge of D7 in combination with the teaching of e.g. D5 with respect to peptide vaccine based on novel epitopes resulting from a frameshift mutation, taking further into account the teaching of D1 concerning the generation of useful novel sequences after a frameshift.

9. **Invention 3:** referring to the frameshift mutation in the human FADD-homologous ICE/CED3-like protease gene; SEQ ID NOs:128-133 .

The peptides according to this invention are not based on any experimental work. The specified sequences ID NOs 128-133 comprising either NLSSLLI or TCLPF appear to be new, but an inventive step is at present not acknowledged, as it has not been demonstrated that the peptides solve any technical problem. CED-3 and and an homologue are known. The CED-3 gene encodes the cell death protease (see e.g. D6). A cancer has not been specified in the description directly linked to the CED-3 gene. However, in view of the prior art knowledge about the importance of frameshift mutation in simple repeat sequences (nucleotide tracks) an inventive step for **claim 4 and part of claims 1, 16 and 34** is not acknowledged.

With respect to the (indirectly depending) **claims 17-33** it is considered that these claims in are obvious to the skilled person having the knowledge of D6 in combination with the teaching of e.g. D5 with respect to peptide vaccine based on novel epitopes resulting from a frameshift mutation.

Invention 12: referring to the frameshift mutation in the human cysteine protease (ICErel-III) gene; SEQ ID NOs:394-398 and 459. For the same reasoning it is considered that **claim 13, part of claims 1, 16 and 34 and** the depending claims lack an inventive step.

10. **Invention 4:** referring to the frameshift mutation in the human putative mismatch repair/binding protein (hMSH3) gene; SEQ ID NOs:134-147.
Invention 6: referring to the frameshift mutation in the human hMSH6 gene; SEQ ID NOs:200-203 and 293-297.

D8 and D9 have reported that nonselected colecteral and gastric cancers of the MMP contain somatic slippage-related frameshift mutation in hMSH3 and hMSH6, harboring an $(A)_8$ and a $(C)_8$ track. The peptides of **claims 5 and 7 and part of claims 1, 16 and 34** are considered to be obvious to the skilled person in the absence of any demonstrated special effect.

With respect to the (indirectly depending) **claims 17-33** it is considered that these claims in are obvious to the skilled person having the knowledge of D7 in combination with the teaching of e.g. D5 with respect to peptide vaccine based on novel epitopes resulting from a frameshift mutation.

11. **Invention 5:** referring to the frameshift mutation in the human neurofibromin (NF1) gene; SEQ ID NOs:176-181.

D12 has referred to a frameshift in the GTPase-activating-protein-related domain and loss of two codons toward the 3' end of the gene; the frameshift by a single base deletion leads to a protein truncated early in the GAP-related domain. In view of the disclosure of D12 it is therefore considered that the peptides of **claim 6 and part of claims 1, 16 and 34** do not involve an inventive step.

With respect to the (indirectly depending) **claims 17-33** it is considered that these claims in are obvious to the skilled person having the knowledge of D12 in combination with the teaching of e.g. D5 with respect to peptide vaccine based on novel epitopes resulting from a frameshift mutation.

12. **Invention 7:** referring to the frameshift mutation in the human TGF-ß induced gene product (BIGH3) gene; SEQ ID NOs:227-232.

The specifying of the peptides of this invention is apparently based on a frameshift in a simple repeat sequence within the known sequence of the BIGH3 gene. In the absence of any special effect demonstrated by the peptides of **claim 8 and part of claims 1, 16 and 34** an inventive step is not acknowledged. The same reasoning applies to **claims 17-33**.

13. **Invention 8:** referring to the frameshift mutation in the human protein-tyrosine kinase (JAK1) gene; SEQ ID NOs:267-271.
Invention 9: referring to the frameshift mutation in the human protein-tyrosine kinase (JAK3) gene; SEQ ID NOs:272-279.

Janus kinase (JAK) nonreceptor tyrosine kinases are essential in signalling by the interferons and other cytokines. JAK1 is thought to phosphorylate the IFN-γR1 subunit of the IFN-γ receptor, creating a docking site for STAT1. JAK3 has an essential role in lymphoid development. In the absence of any special effect demonstrated by the peptides of **claims 9 and 10 and part of claims 1, 16 and 34** an inventive step is not acknowledged. The same reasoning applies to **claims 17-33**.

14. **Invention 10:** referring to the frameshift mutation in the human retinoblastoma related protein (p107) gene; SEQ ID NOs:310-313.

The p107 gene is a close relative of the retinoblastoma tumor suppressor gene (see D13). In the absence of any special effect demonstrated by the peptides of **claim 11 and part of claims 1, 16 and 34** an inventive step is not acknowledged. The same reasoning applies to **claims 17-33**.

15. **Invention 11:** referring to the frameshift mutation in the human malignant melanoma metastasis-suppressor (hKiSS-1) gene; SEQ ID NOs:328-334.

KiSS-1 is a metastasis suppressor gene: see D14. In the absence of any special effect demonstrated by the peptides of **claim 12 and part of claims 1, 16 and 34** an inventive step is not acknowledged. The same reasoning applies to **claims 17-33**.

16. **Invention 13:** referring to the frameshift mutation in the human BRCA1-associated RING domain protein (BARD1) gene; SEQ ID NOs:404-417.

D8 already referred to an analysis of BRCA1 suppressor gene containing an $(A)_8$ repeat in the coding region (see page 4421, left column): reference is made to a frameshift with low frequency (see discussion of D8). Moreover, mutations in the BARD1 gene have also been described (see D15). In the absence of any special effect demonstrated by the peptides of **claim 14 and part of claims 1, 16 and 34** an inventive step is not acknowledged. The same reasoning applies to **claims 17-33**.

17. **Invention 14:** referring to the frameshift mutation in the human DPC4 gene; SEQ ID NOs:429-437.

DPC4 (Smad4) is a candidate suppressor gene shown to be inactivated in half of adenocarcinomas. A study of mutants has been disclosed (see D16). In the absence of any special effect demonstrated by the peptides of **claim 15 and part of claims 1, 16 and 34** an inventive step is not acknowledged. The same reasoning applies to **claims 17-33**.

Re Item VI

18. Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 9910382	04.03.99	26.08.98	27.08.97

It is noted that this document may in the regional european phase be cited with respect to novelty under Article 54(3)(4) EPC.

Re Item VII

Certain defects in the international application

19. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art

disclosed in the documents D1 and D5 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

20. **Claim 24**: the reference in this claim to PCT/NO92/00032 (WO 92/14756) introduces unclarity, as the claim itself should be clear und its scope defined (Article 6 PCT).

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CLAIMS

1. A peptide that

a) is at least 8 amino acids long and is a fragment of a mutant protein arising from a frameshift mutation in a gene of a cancer cell;

and

b) consists of at least one amino acid of the mutant part of a protein sequence encoded by said gene;

and

c) comprises 0-10 amino acids from the carboxyl terminus of the normal part of the protein sequence preceding the amino terminus of the mutant sequence and may further extend to the carboxyl terminus of the mutant part of the protein as determined by a new stop codon generated by the frameshift mutation;

and

d) induces, either in its full length or after processing by antigen presenting cell, T cell responses;

characterised in that the mutant part of the protein has a sequence chosen from the sequences of the sequence identity nos 1-459.

2. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the BAX gene.

3. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the TGF-β-RII gene.

4. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human FADD-homologous ICE/CED-3-like protease gene.

AMENDED SHEET

5. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human putative mismatch repair/binding protein (hMSH3) gene.

6. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human neurofibromin (NF1) gene.

7. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human hMSH6 gene.

8. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human transforming growth factor-beta induced gene product (BIGH3).

9. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human protein-tyrosine kinase (JAK1) gene.

10. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human protein-tyrosine kinase (JAK3) gene.

11. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human retinoblastoma related protein (p107) gene.

12. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human malignant melanoma metastasis-supressor (hKiSS-1) gene.

13. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human cysteine protease (ICE rel-III) gene.

14. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human BRCA1-associated RING domain protein (BARD1) gene.

15. A peptide according to claim 1 characterised in that it arises from a frameshift mutation in the Human DPC4 gene.

16. A peptide according to claim 1 characterised in that it is 8-25 amino acids long, 9-20 amino acids long, 9-16 amino acids long, 8-12 amino acids long, 20-25 amino acids long, 9 amino acids long, 12 amino acids long, or 13 amino acids long.

17. A pharmaceutical composition comprising a peptide according to any of the above claims or a mutant protein as described in claim 1, and a pharmaceutically acceptable carrier or diluent.

18. A cancer vaccine comprising a peptide according to any of the claims 1-16, or a mutant protein as described in claim 1, and a pharmaceutically acceptable carrier or diluent.

19. Use of a peptide according to any of the claims 1-16, or a mutant protein as described in claim 1, for the preparation of a pharmaceutical composition for treatment or prophylaxis of cancer.

20. A method for vaccination of a person disposed for or afflicted with cancer, consisting of administering at least one peptide according to the claims 1-16, or a mutant protein as described in claim 1, one or more times, in an amount sufficient for induction of specific T-cell immunity to the mutant protein or fragment thereof.

21. A method according to claim 20 wherein the amount of the peptide or protein is in the range of 1 microgram (1 µg) to 1 gram (1g) and preferentially in the range of 1 microgram (1 µg) to 1 milligram (1 mg) for each administration.

22. A method for treatment of a patient afflicted with cancer by stimulating *in vivo* or *ex vivo* with a peptide according to any of claims 1-16, or with a mutant protein as described in claim 1.

23. A method according to claim 22 wherein the amount of peptide or protein used is in the range of 1 microgram (1 µg) to 1 gram (1g) and preferentially in the range of 1 microgram (1 µg) to 1 milligram (1 mg) for each administration.

24. A pharmaceutical composition or vaccine composition comprising a combination of at least one peptide according to claims 1-16, or a mutant protein as described in claim 1, and at least one peptide according to PCT/NO92/00032.

25. An isolated DNA sequence encoding a peptide which is a fragment as described in claim 1.

26. An isolated DNA sequence according to claim 25, which encodes a fragment of a protein having a sequence selected from: seq. id. nos. 1-21, seq. id. no. 428, seq. id. no. 438 and seq. id. nos. 456-458, or variants thereof.

27. An isolated DNA sequence according to claim 25, which encodes a fragment of a protein having a sequence selected from: seq. id. nos. 22-427, seq. id. nos. 429-437, seq. id. nos. 439-455 and seq. id. no. 459, or variants thereof.

28. Use of a DNA sequence according to any of the claims 24-26, or of a DNA sequence encoding a protein as described in claim 1, for the preparation of a pharmaceutical composition for treatment or prophylaxis of cancer.

29. Method for treatment of a person disposed for or afflicted with cancer, by stimulating *in vivo* or *ex vivo* with DNA sequences according to the claims 25-27, or with a DNA sequence encoding a protein as described in claim 1.

30. A vector (e.g. plasmid or virus vector) comprising the DNA sequence of claim 25.

31. A vector according to claim 30 wherein the vector is an *E.Coli* plasmid, a Listeria vector or a viral vector (e.g. an orthopox virus, a xanary virus, a capripox virus, a suipox virus, a vaccinia virus, a baculovirus, a human adenovirus, an SV40 virus or a bovine papilloma virus).

32. Use of a vector according to claim 30, or of a vector encoding a protein as described in claim 1, for the preparation of a pharmaceutical composition for treatment or prophylaxis of cancer.

33. Method for treatment of a person disposed for or afflicted with cancer, by stimulating *in vivo* or *ex vivo* with a vector according to claim 30, or with a vector encoding a protein according to claim 1.

34. A peptide according to any of claims 1 to 16, a mutant protein as described in claim 1, a pharmaceutical composition according to claim 17 or 24, a vaccine according to claim 18 or claim 24, a DNA sequence according to any of claims 25 to 27, a DNA sequence encoding a protein as described in claim 1, or a vector as described in any of claims 32 to 34; for use in therapy.

AMENDED SHEET

P9802 PCT

PATENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LILLEGRAVEN, Rita
Norsk Hydro ASA
N-0240 Oslo
NORVEGE

Fax no. 47 22 78 23 08

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

kopi FAEnklan sendt 21/9-0

Date of mailing *(day/month/year)*: 19. 09. 00

Applicant's or agent's file reference	IMPORTANT NOTIFICATION	
P9802		
International application No. PCT/NO99/00143	International filing date *(day/month/year)* 03/05/1999	Priority date *(day/month/year)* 08/05/1998
Applicant NORSK HYDRO ASA et al.		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vullo, C Tel.+49 89 2399-8061

Form PCT/IPEA/416 (July 1992)

PCT/NO99/00143
P9802 PCT

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

LILLEGRAVEN, Rita
Norsk Hydro ASA
N-0240 Oslo
NORVÈGE

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
23 September 1999 (23.09.99)	
Applicant's or agent's file reference	**International application No.**
P9802	PCT/NO99/00143

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

NORSK HYDRO ASA (for all designated States except US)
GAUDERNACK, Gustav et al (for US)

International filing date	:	03 May 1999 (03.05.99)
Priority date(s) claimed	:	08 May 1998 (08.05.98)
Date of receipt of the record copy by the International Bureau	:	16 September 1999 (16.09.99)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] confirmation of precautionary designations
- [ ] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Marie-José Devillard

Telephone No. (41-22) 338.83.38

Search Report for Norwegian appl. no

Granskningsrapport for søknad nr. 19982097

Kategori	Framtrukne publikasjoner: Cited references
X	**Rampino et al. (1997), Science 275:967-969** **(Hele dokumentet) = Whole document**
X	**Yamamoto et al. (1998, mars), Cancer Research 58:997-1003** **(Hele dokumentet)**
X	**Markowitz et al. (1995), Science 268:1336-1338** **(Hele dokumentet)**
X	**Gaudernack (1996), Immunotechnology 2:3-9** **(Hele dokumentet)**
X	**Gjertsen et al. (1996), British Journal of Cancer 65:450-453** **(Hele dokumentet)**
X	**Gjertsen et al. (1996), British Journal of Cancer 74:1828-1833** **(Hele dokumentet)**
X	**Gjertsen et al. (1997), Int. J. Cancer 72:784-790** **(Hele dokumentet)**
X	**Gjertsen et al. (1998), Vox Sanguinis 74(suppl. 2):489-495** **(Hele dokumentet)**
X	**WO 92/14756**

Dokumentkategori:
X: særlig relevant = document of particular relevance
Y: særlig relevant dersom det kombineres med annet dokument i samme kategori
A: bakgrunnsteknikk
D: anført i beskrivelsen
P : dokument med tidligere prioritet (PL § 2.2.2)

&: publikasjon i samme patentfamilie

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO 99/00143

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07K 14/435, A61K 38/17, A61P 35/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07K, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9910382 A1 (NORSK HYDRO ASA), 4 March 1999 (04.03.99) --	1-32
X	WO 9712992 A2 (ROYAL NETHERLANDS ACADEMY OF ARTS AND SCIENCES ET AL), 10 April 1997 (10.04.97), see the claims and page 34 --	1-34
X	WO 9618409 A1 (THE SCRIPPS RESEARCH INSTITUTE), 20 June 1996 (20.06.96), see the claims --	1-34
A	WO 9532731 A2 (THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD ET AL), 7 December 1995 (07.12.95) --	1-34

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2000	13 -01- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/ELY Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.
PCT/NO 99/00143

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9910382 A1	04/03/99	AU 9367798 A	16/03/99
		GB 2328689 A	03/03/99
		GB 9718110 D	00/00/00
WO 9712992 A2	10/04/97	AU 7142796 A	28/04/97
		GB 9520080 D	00/00/00
		US 5958684 A	28/09/99
WO 9618409 A1	20/06/96	AU 4600796 A	03/07/96
		CA 2207736 A	20/06/96
		EP 0793501 A	10/09/97
		FI 972514 A	12/08/97
		JP 10510988 T	27/10/98
		NO 972729 A	13/08/97
WO 9532731 A2	07/12/95	AU 2623795 A	21/12/95
		EP 0762891 A	19/03/97
		GB 9410922 D	00/00/00
		JP 10504702 T	12/05/98

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 January 2000 (06.01.00)	
International application No. PCT/NO99/00143	**Applicant's or agent's file reference** P9802
International filing date (day/month/year) 03 May 1999 (03.05.99)	**Priority date** (day/month/year) 08 May 1998 (08.05.98)
Applicant GAUDERNACK, Gustav et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 December 1999 (02.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Sean Taylor

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P9802	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/NO 99/00143	International filing date (day/month/year) 3 May 1999	(Earliest) Priority Date (day/month/year) 8 May 1998
Applicant Norsk Hydro ASA et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] Certain claims were found unsearchable (See Box I).

2. [ ] Unity of invention is lacking (See Box II).

3. [ ] The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the title,
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established by this Authority to read as follows:

     Peptides that elicit T, cellurar immunity.

5. With regard to the abstract,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO99/00143

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-20,28 and 32
because they relate to subject matter not required to be searched by this Authority, namely:

See extra sheet.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 17-20,28 and 32 relates to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compound(s)/composition(s).